

# Physical Activity and Risk of Ovarian Cancer: A Prospective Cohort Study in the United States

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## Abstract

Increased physical activity may lower the risk of ovarian cancer by reducing the frequency of ovulation, decreasing body fat, or diminishing chronic inflammation. Previous epidemiological studies examining the association between physical activity and risk of ovarian cancer have been inconsistent. We investigated the association of physical activity with ovarian cancer in a prospective cohort of 27,365 individuals from the Breast Cancer Detection Demonstration Project. During 227,045 person-years of follow-up, 121 cases of ovarian cancer were ascertained. Usual physical activity during the past

year was assessed by a self-administered questionnaire. After adjusting for potential risk factors for ovarian cancer, the relative risks (95% confidence intervals) across increasing quintiles of total physical activity were 1.0, 0.73 (0.43–1.25), 0.84 (0.50–1.40), 0.56 (0.31–1.00), and 0.70 (0.41–1.21), respectively ( $P$  for trend = 0.13). In this prospective cohort study among U.S. women, we found no overall significant association between physical activity and risk of ovarian cancer, although the results are suggestive of an inverse association. (Cancer Epidemiol Biomarkers Prev 2004;13(5):765–70)

## Introduction

Ovarian cancer is the fifth most common cancer among women in the United States. It has a low average 5-year survival rate of ~30% for individuals diagnosed in advanced stages (1). In the United States in 2003, it is estimated that ~25,400 new cases will be diagnosed and ~14,300 ovarian cancer deaths will occur (2).

Physical activity affects various metabolic processes that may play a role in preventing ovarian carcinogenesis, such as decreased exposure to estrogens (3–6) and reduced chronic inflammation (7, 8). As high estrogen levels (9) and chronic inflammation (8) are proposed risk factors for ovarian cancer, it is plausible that physical activity may be associated with a decrease in risk of ovarian cancer. However, previous epidemiological studies have been inconsistent. Five studies reported a suggestive inverse association (10–14), one study noted no association (15), and two studies found a positive association (16, 17). To help resolve this issue, we examined the relationship between physical activity and ovarian cancer among participants in the Breast Cancer Detection Demonstration Project (BCDDP) follow-up cohort.

## Materials and Methods

**Study Population.** The study population was composed of individuals who participated in the BCDDP, a program conducted by the American Cancer Society and the National Cancer Institute designed to detect breast cancer (18). The project had 283,222 original participants who were given breast examinations between 1973 and 1980 in 1 of 29 screening centers in 27 U.S. cities. In 1979, the National Cancer Institute began a follow-up study of 64,182 of the original 283,222 participants. These individuals were all women diagnosed with breast cancer during BCDDP screening ( $n = 4275$ ), all women who had biopsies indicating benign breast disease ( $n = 25,114$ ), all women who had been recommended for a biopsy or surgery but for whom the procedure was not performed ( $n = 9628$ ), and an additional sample of women selected from those who did not undergo nor were recommended for biopsy and who were matched to the women in the above categories on age, time of entry into the screening program, length of participation, ethnicity, and location ( $n = 25,165$ ).

The BCDDP follow-up cohort consisted of four phases. Phase I began in 1979 when a baseline questionnaire was returned. Participants who completed phase I were subsequently mailed follow-up questionnaires during phase II (1987–1989), phase III (1993–1995), and phase IV (1995–1998). The questionnaires were designed to obtain demographic information, update exposures to various potential risk factors, and ascertain any new cancer diagnoses.

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**Analytic Cohort.** Of the 64,182 participants of the BCDDP follow-up cohort, 61,431 (96%) women completed the phase I questionnaire and were therefore eligible for further participation in the study. The phase II questionnaire included questions on physical activity and was regarded as the beginning of follow-up for the current study. It was returned by 51,690 women (84% of the BCDDP follow-up cohort). Of these women, we excluded from the analysis women who had a diagnosis of ovarian cancer before phase II ( $n = 95$ ), women who had a diagnosis of breast cancer before phase II ( $n = 5017$ ), women who had both ovaries removed before phase II ( $n = 10,870$ ), and women who provided inadequate information on physical activity ( $n = 8343$ ). The final analytic cohort consisted of the remaining 27,365 individuals. Of the final analytic cohort, 23,798 (87%) participants completed the phase III questionnaire and 23,058 (84%) participants completed the phase IV questionnaire.

**Case Ascertainment.** A total of 121 cases of incident ovarian cancer were ascertained during follow-up. Cases were identified from the following sources: self-reports in the phase III and IV questionnaires ( $n = 48$ ), medical records ( $n = 1$ ), state cancer registries ( $n = 15$ ), the National Death Index ( $n = 32$ ), and the combination of state cancer registries and the National Death Index ( $n = 25$ ). Pathology reports were sought for all self-reported ovarian cancer during follow-up. Self-reported cancers were regarded as cases only if they were confirmed either by pathology reports or by inclusion in a state cancer registry. Cancers based on only self-report were regarded as noncases. All of the participants in the analytic cohort were linked to state cancer registries. Participant deaths that occurred during follow-up were identified by the National Death Index. The cause of death and any contributing factors were then identified by the death certificate. Using available data, we categorized 89 epithelial ovarian tumors according to histology data reported in medical reports or by the state cancer registries: 33 serous, 16 endometrioid, 16 papillary, 16 adenocarcinoma, 4 mucinous, 3 clear cell, and 1 unclassified. The histology of the 32 cases identified only through the National Death Index was not available to us.

**Physical Activity Assessment.** Physical activity was assessed in the phase II questionnaire. Individuals were asked to consider a typical weekday and a typical weekend day for the past year and to estimate how many hours per day they engaged in sleeping, light activity, moderate activity, and vigorous activity, with the number of hours summing to 24. Examples of activities for each of the different categories were listed in the questionnaire to serve as a guideline. Light activity included sitting, working in an office, watching TV, and driving a car. Moderate activity included light housework, hiking, golf, and light sports. Vigorous activity included heavy housework, strenuous sports/exercise, and aerobics.

A set of predefined standards was devised to include only plausible ranges of activity values in the analysis. Participants who reported implausible activity data or who gave no response were considered to have inadequate activity data and were excluded from the study population, as mentioned previously. Acceptable

ranges of daily activity were established for each category: sleep, 4–18 h; light activity, 0–20 h; moderate activity, 0–18 h; and vigorous activity, 0–18 h. For a response to be considered plausible, the total number of hours across all of the categories had to be between 20 and 28, the reported usual number of hours spent sleeping had to be within its acceptable range, and the hours reportedly engaged in light, moderate, and vigorous activity all had to be either within the acceptable range or left blank (in which case a value of zero was assumed).

Adjusted values were calculated for each activity type to represent the reported hours proportioned to 24 h. This was done for the reported hours for both a typical weekday and a typical weekend day. The adjusted values were used to create a physical activity index (PAI) calculated from the relative metabolic equivalent task units (MET) required of each type of activity. One MET is considered equivalent to the energy expended while sitting quietly (3.5 ml O<sub>2</sub>/kg/min; Ref. 19). The PAI was created by using the following formula for both weekend and weekday adjusted physical activity values:

$$\begin{aligned} \text{PAI for a usual day} = & (\text{hours of sleep} * 1) \\ & + (\text{hours of light physical activity} * 2) \\ & + (\text{hours of moderate physical activity} * 4) \\ & + (\text{hours of vigorous physical activity} * 6) \end{aligned}$$

A weighted PAI index was calculated using both weekend and weekday MET values to estimate a daily average value of physical activity, expressed in MET units. This was calculated as:

$$\text{PAI} = [(\text{weekday PAI} * 5) + (\text{weekend day PAI} * 2)] / 7.$$

The number of hours spent in vigorous activity was used as an additional measure of physical activity. The methods used to calculate the physical activity variables are based on previous work in this cohort (20).

**Statistical Analysis.** Relative risks (RRs) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression, with person-years of observation employed as the underlying time metric. Events were defined as incident cases of ovarian cancer. The number of person-years contributed by each individual was defined as the number of years between the date of completion of the phase II questionnaire and the exit date. The exit date was set to reflect whichever event occurred first: an ovarian cancer diagnosis, a bilateral oophorectomy procedure, death, the completion of the phase IV questionnaire, or the end of study. The participants who were lost to follow-up had an end of study date assigned as either the date of last contact in phase IV or the date of the last completed questionnaire plus the mean time between the completion dates of successive questionnaires, whichever was most appropriate. We only included events from the National Death Index and state cancer registries if they occurred before the end of study date. The proportional hazards model assumption was tested by including the cross-product term of physical activity and follow-up time in the multivariate model.

The assumption of proportional hazards was not violated with physical activity expressed in PAI values ( $P = 0.20$ ) or with physical activity expressed in average hours of daily vigorous activity ( $P = 0.47$ ).

The values of total activity (measured by the PAI index) were divided into quintiles of 34.0–48.4, 48.5–54.3, 54.4–59.0, 59.1–65.01, and 65.02–98.1 MET h/day. Daily average hours of vigorous activity were grouped as follows: those who reported a daily average of 0 h were placed in one category, while those who reported nonzero values were divided into tertiles (0.1–1, 1.1–2, and 2.1–14 h/day).

Most covariate information was obtained from the phase II questionnaire. Body mass index (BMI) was calculated from the reported weight and height at phase II. Duration of hormone replacement therapy (HRT) use was measured as duration of use as of the beginning of phase II. Menopausal status was updated using data from the phase III questionnaire. For women who were premenopausal at the time of hysterectomy and had retained at least one ovary, the date of menopause had to be estimated. If the premenopausal woman was 57 years old or younger at the time of hysterectomy, then age at menopause was set to 57, which was the 75th percentile for age at menopause for the participants in the study. If the woman was older than 57, then the age at menopause was set to the age at hysterectomy (21). Missing and unknown values for covariates were combined into one category, which we will henceforth refer to as unknown.

Three models with different sets of covariates were constructed to examine the association between physical activity and ovarian cancer. The first model was a model adjusted only for age at phase II (<53, 54–58, 59–62, 63–67, or 68+). The second was a multivariate model. This model was adjusted for covariates that were controlled for in the majority of the previous studies on physical activity and ovarian cancer. Such covariates were duration of oral contraceptive use (0, 0.1–2, 2.1+ years, or unknown), duration of HRT (0, 0.1–0.9, 1–2.9, 3.0–6.8, 6.9+ years, or unknown), time-dependent menopausal status (premenopausal, postmenopausal, or unknown), and number of live births (0, 1, 2, or 3+ children), which we will henceforth refer to as parity. Because BMI could represent an intermediate step in the causal pathway linking physical activity to ovarian cancer risk, this variable was not included in the primary multivariate analysis. However, BMI (<21.2, 21.2–22.9, 23.0–24.8, 24.9–27.8, 27.9+ kg/m<sup>2</sup>, or unknown) was included in an additional third model to evaluate the relation of physical activity to ovarian cancer independent of its effect on adiposity. In models examining average daily hours of vigorous activity, an additional adjustment for the average daily number of hours the individual engaged in moderate activity was included to isolate the apparent effect of vigorous activity on the risk of ovarian cancer.

RRs were estimated by hazard ratios with 95% confidence intervals. Tests for a linear trend across increasing quantiles of physical activity were conducted by modeling the median values of the quantiles of physical activity as a continuous variable in the multivariate model. The preset level for all tests of significance was 5%. All  $P$  values were based on two-sided tests.

Effect modification for each covariate was assessed by including the cross-product term of the PAI activity variable and the covariate in the model and by examining the Wald  $\chi^2$  statistic and its  $P$  value for the cross-product term. All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

## Results

During 227,045 person-years of follow-up between 1987 and 1998, 121 incident cases of ovarian cancer were ascertained. The average daily hours of sleep, light activity, moderate activity, and vigorous activity proportioned to a total of 24 h were 7.5, 9.4, 5.9, and 1.2 h, respectively.

The baseline (phase II) characteristics of the cohort by quintile of PAI are presented in Table 1. Those with higher levels of physical activity appeared more likely to be parous, to have a family history of ovarian cancer, and to have a hysterectomy prior to phase II than the less active women. In contrast, those with lower levels of physical activity appeared more likely to use oral contraceptives, to smoke, to have at least some college education, and to have a higher BMI.

The results from the analysis of physical activity (as measured by the PAI index) with ovarian cancer risk are presented in Table 2. No significant association was observed between physical activity and ovarian cancer. However, women in the top four quintiles of physical activity appeared to have a similar modest decrease in risk of ovarian cancer, suggesting the possibility of a step-like association. After controlling for potential risk factors for ovarian cancer, the RRs were 1.0, 0.73, 0.84, 0.56, and 0.70 (0.41–1.21), for quintiles 1–5, respectively, with  $P_{\text{trend}} = 0.13$ . Further adjustment for BMI had virtually no impact. When we compared women who fell into the second quintile or higher with women in the first quintile, the multivariate RR of ovarian cancer was 0.71 (0.47–1.06).

We also examined the average hours per day that an individual engaged in vigorous physical activity in relation to ovarian cancer risk (Table 3). The multivariate RRs across increasing levels of vigorous activity were 1.0, 1.02, 0.59, and 0.74 (0.42–1.29), with  $P_{\text{trend}} = 0.17$ . This is also suggestive of a step-like relation of physical activity on an individual's risk of ovarian cancer.

The association of physical activity with ovarian cancer did not differ by the following: age, menopausal status, oral contraceptive use, HRT, family history, or BMI. When we examined the association between physical activity and ovarian cancer risk within strata of women defined by parity, we found a suggestion of effect modification. Among parous women ( $n = 23,874$ ; 103 incident cases of ovarian cancer) but not among nulliparous women, we observed an inverse association between physical activity and ovarian cancer. The multivariate RRs across increasing quintiles of physical activity among parous women were 1.0, 0.68 (0.39–1.19), 0.62 (0.35–1.10), 0.46 (0.25–0.87), and 0.57 (0.32–1.02);  $P_{\text{trend}} = 0.03$ ,  $P_{\text{interaction}} = 0.03$ . The association between physical activity and ovarian cancer among nulliparous women was inconclusive due to very small

**Table 1. Baseline (phase II) characteristics of the 27,365 BCDDP participants by quintile of PAI**

Characteristics	Quintile of PAI (range)				
	Q1 (34.0–48.4)	Q2 (48.5–54.3)	Q3 (54.4–59.0)	Q4 (59.1–65.01)	Q5 (65.02–98.1)
Number of participants	5519	5522	5440	5487	5397
Physical activity (h/day)					
Sleep	7.8	7.6	7.5	7.4	7.1
Light	14.3	11.6	9.1	7.2	4.8
Moderate	1.8	4.4	6.6	7.9	8.9
Vigorous	0.1	0.4	0.7	1.4	3.3
Age (years)	61.5	61.0	61.2	60.8	60.9
Age at menarche (years)	12.7	12.7	12.8	12.8	12.9
Age at menopause (years)*	52.2	52.4	52.3	52.5	52.4
Ever used oral contraceptives (%)	34.2	33.6	33.6	33.4	31.4
Oral contraceptive use duration among users (years)	4.1	3.7	3.8	3.6	4.0
Parous (%)	84.1	86.6	88.2	88.2	89.2
Number of children (among the parous only)	2.8	2.8	2.9	2.9	3.0
HRT (%)	45.1	45.0	44.4	45.4	42.9
Duration of HRT among users only (months)	57.7	59.8	57.9	56.7	56.5
Hysterectomy (%)	26.5	26.3	28.0	28.3	29.4
Race (%)†					
White	90.6	90.0	90.3	89.7	86.8
Asian	4.1	4.8	3.9	4.3	4.8
Black	3.2	2.6	3.0	3.0	4.5
Hispanic	1.1	1.6	1.6	1.7	2.1
Other	0.9	1.0	1.2	1.2	1.8
Height (in.)	64.3	64.2	64.2	64.2	64.1
Weight (lb.)	143.1	140.9	140.8	139.7	139.7
BMI (kg/m <sup>2</sup> )	25.1	24.7	24.7	24.5	24.3
Family history of ovarian cancer (%)	4.6	5.4	5.3	5.6	6.0
Ever smoked (%)	47.9	45.3	43.0	43.0	41.7
Education > high school (%)	56.1	50.9	47.9	47.7	43.1

Note: All values (except age) were standardized to the age distribution of the cohort.

\*Postmenopausal women only.

†Percentages may not sum to 100 because of rounding and/or missing data.

numbers ( $n = 18$  cases). Thus, our results regarding a possible effect modification of the physical activity and ovarian cancer association by parity must be interpreted with caution.

## Discussion

In this cohort of U.S. women, we found no overall significant association between physical activity and risk of ovarian cancer, although the results are suggestive of an inverse association.

One particular strength of the current study is its prospective design, which precluded recall and selection

bias. In addition, our assessment of physical activity was comprehensive because we accounted for the frequency and duration of physical activity. The range of values for PAI was large (34.0–98.1 MET h/day), indicating that the variability in exposure to physical activity likely was high. In addition, we adjusted for several potential risk factors for ovarian cancer, thereby lessening the potential for confounding.

Our study also had some limitations. Although the cohort was large, the number of incident cases was relatively small, limiting the statistical power of the analysis. In addition, the physical activity information was self-reported and we have no information regarding the validity of our measure of physical activity.

**Table 2. RR of ovarian cancer in relation to physical activity expressed in quintiles of PAI**

	PAI quintile (range, MET h/day)					P for trend
	Q1 (34.0–48.4)	Q2 (48.5–54.3)	Q3 (54.4–59.0)	Q4 (59.1–65.01)	Q5 (65.02–98.1)	
Cases	33	23	26	17	22	
Person-years	44,646	45,800	45,485	45,825	45,289	
RR (95% confidence interval)						
Age adjusted	1.0	0.69 (0.40–1.17)	0.77 (0.46–1.29)	0.51 (0.28–0.92)	0.66 (0.39–1.14)	0.08
Multivariate	1.0	0.73 (0.43–1.25)	0.84 (0.50–1.40)	0.56 (0.31–1.00)	0.70 (0.41–1.21)	0.13
Multivariate + BMI	1.0	0.73 (0.43–1.25)	0.84 (0.50–1.41)	0.56 (0.31–1.01)	0.71 (0.41–1.22)	0.14

Note: The multivariate model is adjusted for age, menopausal status, duration of oral contraceptive use, duration of HRT, and number of children.



**Table 3. RR of ovarian cancer in relation to physical activity expressed in adjusted usual vigorous activity hours**

	Adjusted usual vigorous activity hours (range, h/day)				<i>P</i> for trend
	0	0.1–1	1.1–2	2–14	
Cases	67	27	11	16	
Person-years	106,949	49,974	32,832	37,290	
RR (95% confidence interval)					
Age adjusted	1.0	0.93 (0.59–1.46)	0.54 (0.29–1.03)	0.67 (0.39–1.16)	0.07
Multivariate	1.0	1.02 (0.65–1.61)	0.59 (0.31–1.13)	0.74 (0.42–1.29)	0.17
Multivariate + BMI	1.0	1.03 (0.66–1.63)	0.60 (0.31–1.14)	0.74 (0.42–1.30)	0.18

Note: The multivariate model is adjusted for age, hours per day of moderate activity, menopausal status, duration of oral contraceptive use, duration of HRT, and number of children.

Although our PAI may be associated with some degree of misclassification of the exposure, data on physical activity were collected prior to the occurrence of ovarian cancer. Hence, the accuracy of reported physical activity should not differ between women with and without subsequent ovarian cancer. In addition, such random misclassification of physical activity would tend to weaken the results but would not produce a suggestive inverse association. Losses to follow-up in our cohort were minimal and thus are unlikely to have introduced substantial bias. As it was not possible to control for breast feeding and total energy intake, we cannot entirely rule out the possibility of confounding by these factors. A further limitation is our inability to distinguish between occupational and recreational types of physical activity.

Our findings are consistent with the results of four case-control studies (10–13) and one cohort study (14) that support an inverse association between physical activity and risk for ovarian cancer. One Chinese case-control study (10) examining total physical activity in relation to ovarian cancer risk observed a strong inverse relation between the two, reporting an odds ratio of 0.54 (0.34–0.87) comparing extreme categories of physical activity. A case-control study from the United States (11) observed a slightly weaker but statistically significant inverse association between recreational physical activity and ovarian cancer [odds ratio comparing extreme categories = 0.73 (0.56–0.94)]. Another U.S. case-control study (12) found no association between recreational physical activity and ovarian cancer, although there was a suggestion of an inverse relation comparing highest to lowest level of recreational physical activity [odds ratio = 0.70 (0.36–1.35); based on 13 cases]. Similarly, an Italian case-control study (13) presented an odds ratio of 0.83 (0.58–1.18) comparing extreme categories of recreational physical activity and an odds ratio of 0.76 (0.48–1.21) comparing extreme categories of occupational physical activity.

A cohort study in Shanghai (14) found a suggestive inverse association between occupation-related energy expenditure and ovarian cancer risk. The standardized incidence ratio for professionals and technical workers with low energy requirements was 132 ( $P < 0.05$ ). However, no clear associations were observed for craftsmen, service workers, and sales workers (standardized incidence ratios = 102, 97, and 98, respectively; all  $P > 0.05$ ). One cohort study in Finland (15) found no significant difference in ovarian cancer risk between

physical education teachers who were assumed to have higher lifetime physical activity levels and language teachers who were assumed to have a lower lifetime physical activity levels.

In contrast, two prospective studies (16, 17) suggest that frequent physical activity may increase the risk of ovarian cancer. One of these studies (16) found a RR of 2.06 (1.24–3.43) comparing high to low levels of recreational physical activity. The other study (17) reported RRs of ovarian cancer for women engaging in 20–30 and >30 MET h/week of 1.84 (1.12–3.02) and 1.27 (0.75–2.14), respectively.

Two studies reported that the association between physical activity and ovarian cancer was suggestively modified by BMI. For lean individuals, defined as having a BMI of <23 kg/m<sup>2</sup> (12) or <25 kg/m<sup>2</sup> (17), any activity participation appeared to be associated with an increased risk of ovarian cancer, whereas for nonlean individuals, increasing physical activity seemed to be associated with a decrease in ovarian cancer risk. We found no effect modification by BMI among lean individuals (BMI < 23.8 kg/m<sup>2</sup>) versus nonlean individuals in our study.

Physical activity may decrease risk of ovarian cancer by decreasing exposure to estrogen. Physical activity inhibits ovulation temporarily, although the activity likely must be very strenuous and frequent to achieve this (3, 22). In addition, regular physical activity may lengthen ovulatory cycles (4), thereby decreasing lifetime exposure to endogenous estrogens. Physical activity also leads to decreased body fat, which may cause lower levels of extraglandular estrogen production (5, 23). Moreover, increased physical activity may reduce chronic inflammation (7), which may play a role in the development of ovarian cancer (8, 24).

Previous studies on physical activity and risk of ovarian cancer have not addressed effect modification by parity. The mechanism for the apparent effect modification of the physical activity and ovarian cancer relation by parity observed in our study is unclear. One possibility, apart from chance, is that decreased exposure to estrogen may represent an etiologically significant pathway linking greater physical activity with reduced risk of ovarian cancer among parous women only. In contrast, ovarian cancers among nulliparous women may be etiologically less related directly to estrogen stimulation. This testable hypothesis may be explored in future studies of ovarian carcinogenesis.

In conclusion, we found a suggestion of an inverse association between physical activity and ovarian cancer

risk in this cohort of U.S. women. Our data are compatible with the possibility that the apparent protective effect of physical activity on ovarian cancer risk is limited to parous women.

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